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Pharmacological treatment of alcohol dependence: Target symptoms and target mechanisms

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Abstract

Alcoholism is a major public health problem and resembles, in many ways, other chronic relapsing medical conditions. At least 2 separate dimensions of its symptomatology offer targetable pathophysiological mechanisms. Systems that mediate positive reinforcement by alcohol are likely important targets in early stages of the disease, particularly in genetically susceptible individuals. In contrast, long term neuroadaptive changes caused by chronic alcohol use primarily appear to affect systems mediating negative affective states, and gain importance following a prolonged history of dependence. Feasibility of pharmacological treatment in alcoholism has been demonstrated by a first wave of drugs which consists of 3 currently approved medications, the aldehyde dehydrogenase blocker disulfiram, the opioid antagonist naltrexone (NTX) and the functional glutamate antagonist acamprosate (ACM). The treatment toolkit is likely to be expanded in the near future. This will improve overall efficacy and allow individualized treatment, ultimately taking in account the patient's genetic makeup. In a second wave, early human efficacy data are available for the 5HT3 antagonist ondansetron, the GABA-B agonist baclofen and the anticonvulsant topiramate. The third wave is comprised of compounds predicted to be effective based on a battery of animal models. Using such models, a short list of additional targets has accumulated sufficient preclinical validation to merit clinical development. These include the cannabinoid CB1 receptor, receptors modulating glutamatergic transmission (mGluR2, 3 and 5), and receptors for stress-related neuropeptides corticotropin releasing factor (CRF), neuropeptide Y (NPY) and nociceptin. Once novel treatments are developed, the field faces a major challenge to assure their delivery to patients.
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Keywords: Pharmacological treatment; Alcohol dependence; Target symptoms; Target mechanisms

Contents

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1. Alcohol dependence—a chronic relapsing disease

Substance use disorders continue to be viewed by many as defects of character not amenable to medical treatments. One of the objectives of the present paper is to reinforce the point so well argued by others (McLellan et al., 2000) that drug and alcohol dependence are, in fact, chronic relapsing disorders which share numerous characteristics with other chronic relapsing medical conditions such as hypertension, diabetes or asthma. While it is true that alcoholism cannot be treated without regard for its social and behavioral context, this is also true of other chronic relapsing medical conditions. Similar to other chronic relapsing disorders, solid evidence is available today that pharmacological treatments can improve clinically relevant outcomes in alcoholism. This is exemplified by meta-analyses demonstrating the ability of such treatments to prolong the time to relapse following cessation of heavy drinking, or to decrease the number of heavy drinking days (Bouza et al., 2004).

A medical approach to alcoholism treatment offers an established framework for developing and implementing evidence-based, rather than opinion-based treatment strategies. An additional appeal of this approach is that it offers an alternative to moralizing and confrontational approaches, which are neither effective (Hester & Miller, 2003) nor ethically attractive. The major objectives of this review are (1) to define the clinical manifestations of alcoholism that might offer meaningful treatment targets, (2) to summarize the evidence for a first wave of pharmacological treatments already available today, (3) to review a second wave of candidate treatments for which initial clinical evidence has been obtained and which are in development, and (4) to review a selection of third wave compounds for which clinical data are lacking, yet compelling preclinical evidence points to attractive novel candidate treatment targets. As a backdrop for these third-wave compounds, we will outline some key animal models which facilitate discovery and preclinical validation of novel candidate treatments.

1.1. Targetable clinical phenomena—susceptibility factors, history of dependence, and the relapse process

Tolerance following prolonged use and withdrawal symptoms upon discontinuation are still commonly perceived as core phenomena of alcohol dependence. They may clearly be part of the syndrome, but are in fact neither necessary nor sufficient to establish a diagnosis. Current diagnostic criteria (American Psychiatric Association, 1994) reflect the multidimensional nature of alcoholism. A diagnosis of alcohol dependence is considered to be present if 3 or more of the criteria in Table 1 are present during a 12-month period. With this, it is apparent that 2

Table 1
The Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, fourth edition (*DSM-IV*) defines **alcohol dependence**, to be equated with alcoholism, as:

- A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:
  1. Tolerance, as defined by either of the following:
     - A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
     - Markedly diminished effect with continued use of the same amount of substance.
  2. Withdrawal, as manifested by either of the following:
     - The characteristic withdrawal syndrome for the substance.
     - The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
  3. The substance is often taken in larger amounts or over a longer period than was intended.
  4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
  5. A great deal of time is spent in activities to obtain the substance, use the substance, or recover from its effects.
  6. Important social, occupational or recreational activities are given up or reduced because of substance use.
  7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

[*DSM-IV, Diagnostic and Statistical Manual of Mental Disorders*, ed. 4. Washington, DC: American Psychiatric Association (AMA). 1994].

individuals may receive a diagnosis of alcohol dependence without sharing a single symptom. This allows for the variability in clinical presentation caused by external factors and/or by the progression of the disease in an individual. However, with this, the diagnostic category also becomes broad. Therefore, a key issue is whether a diagnosis of alcoholism reflects a relatively homogeneous phenotype, likely to be uniformly sensitive to the same therapeutics. As will be shown below, this does not seem to be the case.

A further potential weakness of the current diagnostic framework from a treatment-development perspective is that it blends physiological phenomena (tolerance and withdrawal), behavioral manifestations (alcohol-seeking, loss of control), and social consequences (impairment of function). Although clinically justified, this does not facilitate efforts to develop novel treatments. From a treatment-development perspective, alcohol dependence is a disorder in which pathological affective states, dysfunctional cognitive processing and rigidly stereotyped habits evolve over years of alcohol use, and lead to a restricted, maladaptive range of behaviors. This is a long term process whose outcome, in terms of social psychology, is that the subject ultimately fails to self-regulate (Bandura, 1977; Bandura & Locke, 2003). This is characterized by a pattern in which the subject may be successful in maintaining limited periods of abstinence, but these are repeatedly disrupted by destructive relapse episodes during which behavioral control is lost. The objective of any candidate treatment, be it behavioral or pharmacological, is to modulate the dysregulated motivations and cognitions in ways which will help the patient regain ability for self-regulation, or, to invoke a key concept, improve "self-efficacy" (Bandura & Locke, 2003). A simple conceptual framework for how treatments can tilt the balance of behavioral choices in a favorable direction is given in Fig. 1.

Until recently, treatment development efforts at the preclinical stage were rarely guided by available clinical insights into the relapse process. This is rapidly changing. At least 2 critical lessons have been learned. The first concerns the context in which treatment development must be carried out. Pre-existing genetic susceptibility factors are clearly present in many alcoholics (Goldman et al., 2005). They are important for the initiation phase of this disease and may also contribute to maintaining the dependent state in later stages in some individuals. In addition, it is now clear that a history of prolonged alcohol abuse produces neuroadaptive changes which alter the brain in ways which sustain the disease state, and therefore must be considered when evaluating the potential of novel treatment targets (Ulrichsen et al., 1998b; Malcolm et al., 2000; Roberts et al., 2000a; Rimondini et al., 2002, 2003; De Witte et al., 2003). As will be discussed below, this has profound implications for the animal models used to discover and validate novel treatment targets.

Insights into the nature of the relapse process in humans (Brownell et al., 1986) contribute to treatment development. A converging human and animal literature points to 3 categories of stimuli as particularly important for initiating relapse, and thus promising as target mechanisms for treatments. The first of these comprises small, "priming" doses of alcohol itself, given experimentally in preclinical studies (Le et al., 1998), or sampled by patients due to habit, and/or incorrect belief that self-regulation has been re-established after a prolonged period

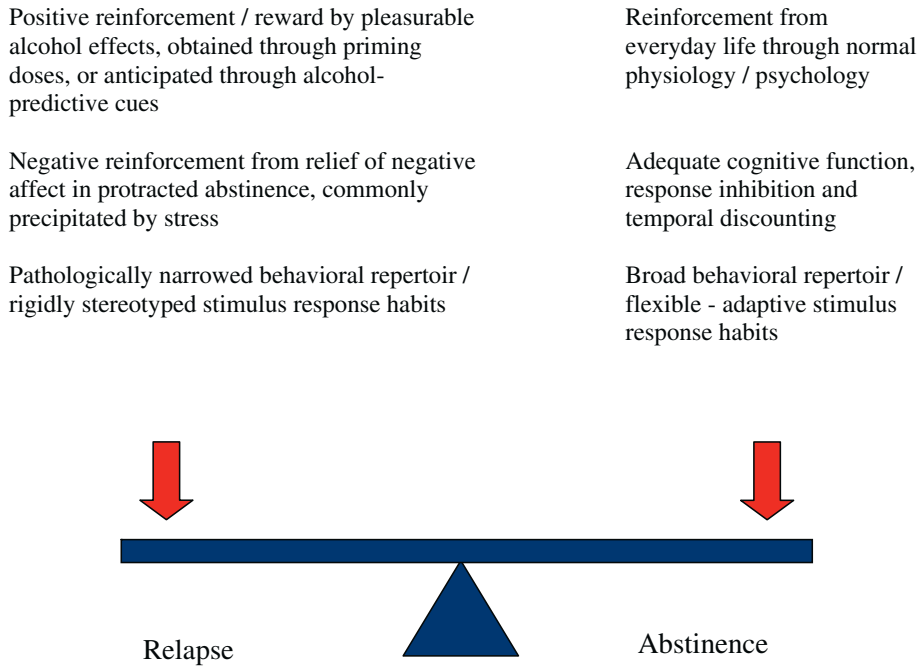

Fig. 1. Broad categories of factors influencing behavioral choices that favor abstinence or withdrawal, respectively. These factors point directly to clinical targets for alcoholism treatments. Any treatment that helps tilt the scales in a favorable direction has clinical potential. Some of the factors listed are likely best addressed by pharmacological treatments, such as, for example, dampening of reward-type/positive reinforcement, or relief-type/negative reinforcement driven craving. Other, such as relearning automated stimulus-response habits, are obviously an ideal target category for behavioral therapies. Evidence is available that pharmacological and behavioral treatments can synergize.

of abstinence. The second category comprises conditioned alcohol-associated stimuli, which can be discrete (cues) or contextual (an environment) in nature (Katner et al., 1999). Finally and perhaps most importantly, negative affect is one of the most common antecedent of relapse in humans (Brownell et al., 1986; McKay, 1999), whereas stress, a powerful trigger of negative affective states, is highly effective in inducing relapse-like behavior in experimental animals (Le et al., 1998). These observations suggest 3 categories of relapse-triggering mechanisms which may be targeted with pharmacological interventions.

Relapse evokes the construct of craving. Although it reflects a subjective state and may be difficult to operationalize, craving is in fact easily recognized by patients themselves, their significant others and experienced clinicians alike. Craving is most likely not a unitary phenomenon. As we will see below, a recently proposed distinction into reward versus relief craving (Heinz et al., 2003) conforms to the categories of relapse triggers outlined above, is consistent with the heterogeneity of alcohol dependence, and generates testable hypotheses about the utility of different pharmacological strategies in different patients.

Relapse mechanisms elicited by alcohol ingestion, conditioned cues, and by stressors provide meaningful and measurable clinical targets for novel treatments. Additional pathophysiological mechanisms also offer potential clinical targets. Perhaps foremost among these is impulsivity (Gerald & Higley, 2002), a markedly impaired inability to inhibit behavior, and a propensity for trading small short term gains for larger long term returns (temporal discounting; Tucker et al., 2002). As we will see below, these traits are highly characteristic of a subgroup of alcoholics with early onset and high heritability, and are worsened by the use of alcohol itself.

We suggest that novel treatments will be generated through an improved understanding of genetic susceptibility factors for alcoholism, of neuroadaptive processes resulting from a history of alcohol use, and of mechanisms through which sampling drug, being exposed to drug-associated stimuli, or experiencing negative affect leads to relapse.

1.2. Heterogeneity of alcohol dependence—implications for treatment development

The clinical targets outlined above are likely to be differentially important across alcohol dependent patients. Alcoholism has a heritability of 50–60% (Goldman et al., 2005), but the inheritance is complex. Early adoption results (Cloninger et al., 1981) which have since been elegantly replicated (Sigvardsson et al., 1996) indicated a marked heterogeneity both of the disease and the inheritance pattern. What was somewhat unfortunately called “Type II” alcoholism is the most distinct form. It is thought to be present in 1/4 to 1/3 of alcohol dependent subjects, although, due to its higher severity, this subtype is enriched in clinical populations. This subtype is first and foremost characterized by an early age of onset, and by high impulsivity and co-morbid antisocial personality traits. This group accounts for most of the heritability (Cloninger, 1987). The remaining population of late onset subjects, called Type I, appears less distinct. Anxious personality traits have been proposed as a characteristic feature, but it is likely that this group is heterogeneous in other relevant dimensions.

The validity of this categorization has been disputed over the years, and several alternative typologies have been proposed. Recent pharmacological treatment results have, however, largely confirmed this distinction, emphasizing the central role of the age-of-onset criterion, and demonstrating the differential response to treatment that can be expected based on diagnostic and pathophysiological heterogeneity. Thus, ondansetron, the 5HT3 antagonist used for chemotherapy-induced nausea, reduces drinking in early-onset patients, but, using exactly the same study design, appears to be ineffective in late-onset subjects (Johnson et al., 2000b). 5HT3 receptors are located on mesolimbic DA terminals and modulate DA release, an action implicated in the positively reinforcing effects of drugs of abuse (Johnson, 2004b). These results are consistent with predictions that alcohol consumption by early-onset alcohol dependent subjects occurs primarily for the positively reinforcing effects of EtOH driven by reward craving. In the remaining majority of subjects, reward craving may play little role, reducing the importance of neural substrates of positive EtOH reinforcement as targets for novel treatments. Other targets, such as those mediating stress-induced relapse, are likely to play a much more important role in this predominant group of patients.

1.3. Co-morbidity with affective and anxiety disorders

More often than not, alcohol dependent patients present with co-morbid psychiatric symptoms, most commonly those affecting mood, anxiety and sleep. These symptoms represent substance-induced disorders which resolve in parallel with withdrawal symptoms, aggregated with independent, often pre-existing mood and anxiety disorders. Although it has been argued for some time that the former category dominates, more recent data suggest that the latter accounts for considerable morbidity, in particular among women (Schuckit & Hesselbrock, 1994; Grant et al., 2004).

The high degree of comorbidity in alcohol dependence prompts the question whether medications for mood and anxiety disorders might also be beneficial for alcoholism per se. This notion became particularly attractive when the selective serotonin reuptake inhibitors (SSRIs) entered the market, and offered a tool that appeared safe for use in alcohol dependence. In particular, this category of drugs, as opposed to their tricyclic predecessors, did not lower seizure thresholds, which is an important safety concern in treatment of alcohol dependent subjects.

One and a half decades of extensive, and at times controversial, research converge on the conclusion that SSRIs ameliorate symptoms of depression and/or anxiety in alcohol dependent patients in much the same way as patients with these disorders but no co-morbid alcoholism. Given appropriate diagnostic work-up, their use in alcohol dependent subjects with co-morbid mood and anxiety symptoms is therefore warranted.

However, despite some initial positive trials, these drugs do not seem to beneficially affect the core symptoms of alcohol dependence (Garbutt et al., 1999; Nunes & Levin, 2004). For this, targeting novel mechanisms seems necessary.

2. The first wave: currently available treatments

2.1. Disulfiram

For many years, disulfiram was the only medication available to aid sobriety. Disulfiram blocks the enzyme aldehyde dehydrogenase, leading to an accumulation of acetaldehyde following intake of alcohol. This in turn causes flushing, shortness of breath, tachycardia, headache and nausea. It has been thought that anticipation of these symptoms would help patients abstain from alcohol. Importantly, the idea is *not* that the patients will actually experience aversive symptoms, and because of them extinguish alcohol use. In fact, the consequences of aldehyde accumulation pose an unacceptable medical risk. Patients who do not understand this, or for other reasons are unable to abstain despite taking the medication are not appropriate candidates for disulfiram therapy.

Despite its widespread use, disulfiram has a limited and largely negative documentation for efficacy. One recent meta analysis (Hester & Miller, 2003) concluded that evidence for its efficacy is lacking. In a more detailed analysis, Berglund et al. (2003) also arrived at the conclusion that evidence for efficacy of disulfiram is lacking overall, but pointed out that some evidence is available for disulfiram being effective when given under supervision. This illustrates the well known fact that compliance is a major issue in using disulfiram. Attempts have been made to circumvent this using depot treatment. Unfortunately, the preparations evaluated to date do not maintain adequate plasma concentrations of disulfiram over time, and therefore, the results have been negative (Berglund et al., 2003).

Overall, disulfiram may be clinically useful for limited periods of time, such as when trying to assess psychiatric co-morbidity in a patient and disentangle it from psychopathology secondary to onoging alcohol use. However, disulfiram does not directly target the core phenomena of alcohol dependence, and is therefore viewed as an outmoded treatment. Disulfiram reduces alcohol drinking by severely punishing drinking bouts. For optimal efficacy, punishment must be applied severely and consistently. Taking this to a logical, but undesirable extreme, it would be more effective and safe to use a biosensor and an electric shock generator.

Ironically, disulfiram may emerge as a treatment for other addictions. It turns out that this compound is also a potent inhibitor of dopamine beta-hydroxylase (DBH), resulting in a blockade of norephinephrine synthesis. Noradrenergic input from the Locus Coeruleus to dopaminergic cell bodies in the Ventral Tegmental Area is required for the phasic firing of these neurons, a firing pattern that releases large amounts of dopamine in the ventral striatum, and is key to the rewarding properties of stimulants and cocaine. Possibly because of this, disulfiram has recently demonstrated efficacy in cocaine dependence through mechanisms unrelated to its effects on alcohol use (Carroll et al., 2004).

2.2. Naltrexone

Naltrexone (NTX) has long been available as an orally available antagonist at opioid receptors, with a relative selectivity for the μ-opioid receptor at lower doses. It was originally studied as a potential treatment for opiate dependence, where it seems to be effective in special cases, but not across the broad range of patients (Kirchmayer et al., 2000). NTX taps into known EtOH actions in a seemingly logical manner. EtOH administration leads to release of endogenous opioid peptides, and one of the downstream effects of this is to activate mesolimbic dopamine (DA) release. This in turn contributes to acute positive reinforcing properties of drugs of abuse (Kreek et al., 2002). Consistant with this chain of events, μ-receptor null-mutant mice do not self-administer EtOH (Roberts et al., 2000b).

Initial clinical evidence for efficacy of NTX in alcohol dependence was generated more than a decade ago (O'Malley et al., 1992; Volpicelli et al., 1992). It has since been replicated in numerous trials, recently reviewed and subjected to meta-analysis in Bouza et al., (2004) and Srisurapanont and Jarusuraisin (2005). Although 1 large negative trial has received considerable attention (Krystal et al., 2001), meta-analyses of available trials, even when the negative study is included in the analysis, unequivocally support NTX efficacy.

The latter of the 2 meta-analyses cited above included 27 randomized controlled trials with NTX. It found that short-term treatment with this drug decreased relapse with a risk ratio (RR) of 0.64. The number needed to treat (NNT), defined as the number of patients that need to be treated to prevent 1 additional bad outcome, is commonly used in evidence-based literature to put efficacy in perspective. For NTX and relapse, the NNT is 7. The corresponding number is much larger, indicating a lower effect size, for many established medical treatments, such as hypertension treatments to prevent stroke, myocardial infarction or premature death, where it ranges between 29 and 86, depending on the age of the patient (Pearce et al., 1998). Furthermore, since retention in treatment is a major challenge in any addiction treatment, it is important to note that NTX significantly improved this outcome. Medium-term treatment of NTX did not yield an equally significant effect with respect to relapse prevention, but was still beneficial on 2 of 4 secondary outcomes, i.e., increased time to first drink, and diminished craving.

The role of concomitant behavioral treatments is commonly discussed in alcoholism treatment, and it is frequently argued as an a priori assumption that pharmacological treatments can at best be adjuncts to an intensive behavioral treatment. Meta-analysis found that for short-term treatment, NTX was not more effective when given together with an intensive behavioral treatment than when the latter treatment component was minimal. In the medium term, on the other hand, an intensive behavioral treatment did augment the ability of NTX to increase time to first drink and decrease craving. A clinically important

possibility is that the main action of behavioral treatments is to augment patient compliance with NTX treatment, a variable that has been found critical in determining the success of this treatment (Volpicelli et al., 1997). An alternative or complementary way of achieving sufficient compliance is offered through administration of a depot-preparation, the efficacy of which has recently been elegantly demonstrated (Garbutt et al., 2005).

Based on the role of endogenous opioids in mediating acute positive reinforcement of EtOH, NTX would be expected to benefit subjects whose disease is mostly characterized by reward craving. By extension, this implies early onset, type II individuals. Although direct evidence for this notion remains to be generated, circumstantial evidence suggests that this is indeed the case. The initial clinical work indicated that NTX may act by blocking the euphorogenic effects of EtOH (Volpicelli et al., 1995). When EtOH was given under laboratory conditions, blockade of the resulting "high" was produced selectively in high-risk, family-history-positive subjects (King et al., 1997). Furthermore, a functional 118G variant allele of the μ-opioid receptor has meanwhile been discovered, which encodes an amino acid substitution that alters the affinity of the receptor for endogenous ligands (Bond et al., 1998). This variant has been associated with alcohol dependence in case-control studies (Bart et al., 2005), and confers a response to EtOH administration characterized by higher subjective feelings of intoxication, stimulation, sedation, and happiness, compared with the wildtype 118A allele (Ray & Hutchison, 2004). To complete the chain of evidence, the 118G allele has recently been found to be a predictor of treatment response to NTX in alcohol dependent subjects (Oslin et al., 2003). Thus, meta-analyses may underestimate the effect size for NTX due to heterogeneity of patients. In an optimal patient population, the effect may in fact both be larger in size and more robust than has been realized, whereas other patient groups may benefit little, diluting overall estimates.

In conclusion, NTX efficacy, and safety is well documented. Promising predictors of positive effect are emerging. Against this background, it is highly disturbing that this drug is not made available to the patients that need it. A recent study found that even addiction medicine specialists prescribe NTX only to 13% of their alcohol dependent patients (Mark et al., 2003). Barriers cited to implementing this evidence based treatment were concerns about patient's ability to comply with it, and/or afford the medication. In fact, however, analysis indicated that prescription rates were predicted by the physicians' perception of NTX efficacy and safety.

2.3. Acamprosate

Multiple lines of evidence suggest that as alcohol dependence develops, a progressive recruitment of a hyperglutamatergic CNS state occurs (Ulrichsen et al., 1998b). Acamprosate (ACM) is a functional glutamate antagonist whose precise molecular mechanisms of action remain unknown. Originally proposed to be a GABA-analogue, it has since been claimed to attenuate NMDA signaling through partial agonism at the spermidine site, and more recently through actions at metabotropic glutamate receptors (Spanagel & Zieglgansberger, 1997; Harris et al., 2002). Importantly, ACM selectively blocks dependence induced drinking (Rimondini et al., 2002), and normalizes the progressive recruitment of elevated extracellular glutamate that occurs with repeated cycles of intoxication and withdrawal (COMBINE Study Research Group., 2003b; De Witte et al., 2003). Perhaps the most elegant demonstration of ACM acting through normalization of a hyperglutamatergic state to date was generated in a different context. It was recently found that null-mutation of the clock gene *per2* results in attenuated expression of the glial glutamate transporter GLAST. This in turn leads to elevated levels of extracellular glutamate, and excessive voluntary EtOH intake. In these mutants, both the elevated glutamate levels and alcohol drinking were normalized by ACM (Spanagel et al., 2005).

Clinical efficacy of ACM is robustly documented in meta-analyses of available studies (Bouza et al., 2004; Mann et al., 2004). The latter of these, a meta-analysis of 17 studies which included 4087 individuals, found that continuous abstinence rates at 6 months were significantly higher in ACM-treated patients compared to placebo (Odds Ratio, 1.47). At 12 months, the overall pooled difference in success rates between ACM and placebo was 13.3%, yielding an NNT of 7.5. Although this number appears to be similar to that for NTX, it is important to bear in mind that different outcome variables seem to be differentially affected by the 2 drugs, making a direct comparison of the effect size difficult. The role of retention in treatment as an important surrogate outcome variable has been mentioned above. In that light, it is important to note that ACM, like NTX, also had a modest but significant beneficial effect on retention.

A possible limitations for clinical use of ACM are the large doses and dosing regimen required. The directions for ACM are two 333-mg tablets 3 times a day. This may impact the efficacy of ACM for the chronic treatment of alcoholism. Furthermore, mechanistic data for ACM's therapeutic efficacy for alcoholism are more limited than those available for NTX. A widely held hypothesis is that ACM might preferentially target relief craving, and pathological brain function arising over time as a result of long-term intoxication and repeated withdrawal episodes (Ulrichsen et al., 1998a; Heinz et al., 2003).

2.4. Combination treatment with naltrexone and acamprosate

If NTX and ACM are each efficacious to an extent that is clinically useful, but overall insufficient, an obvious question is whether their effects might be additive, providing a rationale for combined treatment. This question is at the core of the large, NIAAA sponsored COMBINE study which is currently nearing its completion (COMBINE Study Research Group, 2003a, 2003b). Although COMBINE will provide a rich database capable of addressing numerous important questions, its basic objective has in part already been achieved by a tightly focused European study (Kiefer et al., 2003). In this study, the rank order of survival curves for non-relapse over 3 months was NTX + ACM > NTX > ACM > placebo. Although only some of these

comparisons yielded statistical significance (NTX as well as ACM alone significantly superior to placebo, and the combination superior to either placebo or ACM given alone), this may reflect the somewhat limited power of the study to evaluate all possible comparisons.

The European study thus might seem to supply a rationale for combined treatment, but the issue is in fact more complicated. What this study leaves unanswered, as will the US COMBINE study, is the following question: Is the additive effect of NTX and ACM due to 2 distinct pathophysiologies, which are targeted by each of the drugs, and which co-exist in the same individuals, so that the additivity is present at the level of the individual? Or, alternatively, are different individuals in a heterogeneous patient population uniquely sensitive to 1 drug or the other, such that an additive effect only exists at a group level? An answer to this question is of high clinical importance. The former possibility would provide a rationale for broad implementation of combined treatment. The latter would instead point to the importance of identifying predictors of NTX or ACM response, respectively. A major effort currently underway in Germany promises to address this issue, using functional brain imaging, psychophysiology and pharmacological treatment (Rist et al., 2005; Spanagel & Mann, 2005).

3. The second wave: the near future

3.1. Ondansetron

The introduction of SSRIs and realization of their broad therapeutic spectrum, together with the isolation of serotonergic receptors greatly increased serotonin research during the late 1980s and early 1990s. During this era, it was expected that compounds targeting various components of central 5HT systems would also be evaluated for their ability to affect EtOH drinking. Early studies indicated that SSRIs and the 5HT3 antagonist ondansetron both suppressed various parameters of EtOH drinking in experimental animals. However, SSRIs did so while also suppressing fluid intake and reducing body weight, likely indicative of non-specific actions. Ondansetron, in contrast, seemed to be more selective in its effects (Higgins et al., 1992; Meert, 1993; Tomkins et al., 1995).

Ondansetron was already in human use for nausea, and the first human studies for alcohol use could therefore follow shortly after the initial animal data. The first human trial was carried out by Johnson et al. in Oxford. It appropriately employed consumption of a pint of lager as the laboratory drinking paradigm, and found that pretreatment with ondansetron significantly attenuated several of the subjective pleasurable effects of alcohol, and also decreased the subjective desire to drink, thus indicating an ability to suppress priming induced craving and relapse (Johnson et al., 1993). This was corroborated by subsequent laboratory drinking results by an independent group of investigators, which led these to conclude that reductions in alcohol consumption observed in animals treated with ondansetron may be mediated by increases in subjective intoxication, and/or increases in the aversive effects of alcohol. Only 1 year after the initial experimental drinking study, a small (70 subject) 6 week RCT in non-severe alcoholics was published from Toronto (Sellers et al., 1994). Despite the limited power of this study, reduced drinking approached statistical significance, and achieved significance in some secondary analyses.

The most elegant evidence so far, which not only documents efficacy of ondansetron in alcohol dependence, but also indicates how it may fit into the therapeutic toolkit, appeared in the previously cited study by Johnson et al. (2000b). This study was 11 weeks in duration, and adequate in size. Most importantly, it was stratified by age of onset, based on an a priori prediction that early onset, family history positive subjects would be selectively responsive to the beneficial effects of ondansetron. Notably, this phenotype closely approximates that described as type II alcoholism by Cloninger and Bohman (Cloninger, 1987). As predicted, a robust reduction of self-reported drinking was found in the early-onset group, but not among late-onset patients. The effect size of ondansetron in the early onset group ranged between small to medium for the various outcome measures, but the robustness of the treatment effect was highlighted by its consistency across several outcome measures, and the fact that self-reported reduction in drinking was accompanied by a significant reduction in an objective biomarker of heavy alcohol use, carbohydrate deficient transferring (CDT). This important result has since been independently replicated (Kranzler et al., 2003), which lends it considerable strength. A hint of the underlying mechanism is provided by a secondary analysis of the pivotal Johnson study (Johnson et al., 2002), which indicated that ondansetron reduced subjective craving in early onset, but not in late onset subjects, in whom the lowest ondansetron dose in fact increased craving somewhat. Importantly, drinking correlated with subjective craving, lending support to the hypothesis that ondansetron indeed reduces EtOH use in early onset subjects by suppressing reward-type craving.

Based on theoretical consideration, 2 follow-up trials examined the possibility that ondansetron and NTX, which presumably also targets reward-type craving, might have additive effects. Although positive results have been reported both for self-reported drinking (Johnson et al., 2000a), biomarkers (Ait-Daoud et al., 2001a) and reduction of craving (Ait-Daoud et al., 2001b), the combination has only been compared to placebo, and not to each of the drugs given alone in a full factorial design. It therefore remains unclear whether effects of ondansetron and NTX are, in fact, additive. Although additivity would obviously be useful clinically, it might be argued that a lack thereof would be the strongest evidence that both act by suppressing reward-type craving.

In summary, ondansetron has a reasonably well documented efficacy for early onset alcoholism, with an effect size in the small-to-medium range. It appears safe and well tolerated. Its documented differential effect in early versus late onset alcoholism highlights the need for careful clinical assessment beyond a DSM IV diagnosis of alcohol dependence in choosing optimal treatment for a patient. The optimal patient population for ondansetron likely overlaps with or is the same as that for NTX. A full factorial study similar in design to that of Kiefer et

al. (2003) is needed to assess the relative efficacy of the 2 drugs, and the possibility that they may have additive effects. Considering individual variation in efficacy and tolerability between patients, even in the absence of answers to these questions, ondansetron should be added to the therapeutic toolkit without delay.

3.2. Baclofen

Baclofen is an agonist at the metabotropic GABA-B receptor. It has been on the market for treatment of spasticity for many years, and is thought to act at a spinal level when used for that indication. The first data suggesting that it may be of value for alcoholism treatment appeared 3 decades ago, when the Arvid Carlsson group showed that baclofen blocked alcohol-induced locomotion in mice, and influenced dopamine metabolism in ways consistent with its ability to inhibit the firing of DA-neurons (Cott et al., 1976). Although this finding followed directly on the ground-braking discovery by the same group that dopamine mediates the euphorogenic properties of EtOH in humans (Ahlenius et al., 1973), it was not followed up for some time. The original finding directly implicated that baclofen would reduce EtOH reward and thus voluntary EtOH consumption, yet this prediction was not tested for another 10 years. The prediction was supported when tests were finally performed using Long-Evans rats. The data indicated a selective role of GABA-B but not ionotropic GABA-A receptors in modulation of alcohol intake (Daoust et al., 1987).

For unclear reasons, it then took another decade before this line of work was resumed by Gessa's group in Italy. This time, the effort was much more concerted. In a rapid and logical succession, it was first shown that baclofen reduces withdrawal severity as well as voluntary EtOH consumption in the alcohol preferring Sardinian sP rat (Colombo et al., 2000), and this was rapidly followed by preliminary human efficacy data in an open label safety and tolerability study of 10 male alcoholics (Addolorato et al., 2000).

In this case, the preclinical and clinical data have accumulated in parallel, and appear consistent. In sP rats, baclofen has now also been shown to inhibit acquisition of EtOH consumption (Colombo et al., 2002), to suppress the alcohol deprivation effect, an important model of relapse-like binge drinking (Colombo et al., 2003a), and to suppress motivation to obtain EtOH, measured as operant responding on a previously EtOH associated lever during extinction responding (Colombo et al., 2003b). Suppression of operant responding for EtOH has also been independently reported by a second group in genetically heterogenous Wistar rats, although a detailed analysis in this study indicated that baclofen may equally suppress motivation to obtain sucrose, and thus affect appetitive motivation in general, at least in genetically heterogenous animals without a history of dependence (Anstrom et al., 2003). This is not a major concern. First, for unknown reasons, sweet and EtOH preference are genetically linked, at some concentrations to almost 80% (Belknap et al., 1993). Second, although motivation for sweet and EtOH intake make be equally affected in non-dependent drinking, it is well established that motivation to obtain EtOH is pathologically up-regulated following a history of dependence (Roberts et al., 2000a; Rimondini et al., 2002) or when genetic selection has led to abnormally high EtOH preference (McBride & Li, 1998). A testable prediction is that under either of these conditions, baclofen may more selectively inhibit the motivation to obtain EtOH.

Suppression of operant EtOH self-administration by baclofen is further supported by independent data obtained in C57Bl/6 mice, an inbred line which has a genetically determined high voluntary EtOH consumption and self-administration (Besheer et al., 2004). This careful analysis related efficacy in suppressing EtOH reinforced responding to locomotor-suppressing actions and potentiation of EtOH-induced sedation. Of some concern, doses that suppressed the former also suppressed locomotion, and potentiated sedative actions of non-sedative EtOH doses. Potential sedative side effects and EtOH interactions may pose the most important challenges in developing baclofen or other GABA-B agonists for clinical use in alcohol dependence.

Available clinical data are based on limited numbers of subjects compared to NTX, ACM and ondansetron, but they have evolved in a consistent manner. A small RCT (Addolorato et al., 2002) explored potential efficacy of baclofen for suppression of drinking over 1 month in 39 alcohol dependent subjects. Despite its limited power, the study generated data suggesting that baclofen increased the proportion of subjects totally abstinent from alcohol, increased the number of cumulative abstinence days, and reduced alcohol intake. The drug also decreased measures of craving and of anxiety, but not those of depression. An American follow up study had a more adequate duration (12 weeks), but was carried out in an open-label design without a control condition, and employed an even smaller number of subjects, 9 men and 3 women. Within the considerable limitations of its design, it seemed to support the Italian data.

In summary, on the basis of the available data, baclofen appears to hold considerable promise for treatment of alcohol dependence. This promise needs to be confirmed in an adequately sized RCT of appropriate duration. One such study is now underway at University of North Carolina at Chapel Hill, but it will be some time before it can provide more definitive data. The greatest concern in developing baclofen for clinical use in alcohol dependence is related to its sedative properties, and potential for interactions with EtOH. This is likely a pharmacodynamic class effect, and if problematic could invalidate GABA-B agonism as treatment principle in general. Just as is the case with efficacy, there is no substitute for sufficiently sized clinical trials to answer this crucial question, and results of these will have to be awaited. Despite the original preclinical data of dopaminergic stabilization, the ability of baclofen to reduce measures of anxiety, points to the possibility that is may primarily affect relief-type craving. This in turn would predict a potential for additive effects with a treatment that targets reward-type craving, such as NTX. Preclinical data indeed indicate such a potential for additivity (Stromberg, 2004). Finally, it should be noted that baclofen

may hold potential for treatment of other substance disorders, including opiate, cocaine and nicotine dependence (Cousins et al., 2002).

3.3. Topiramate

Topiramate was identified as an antiepileptic through a screen at the Anticonvulsant Screening Program of the National Institute on Neurological Disorders and Stroke (NINDS). It has by now documented efficacy as monotherapy in adults with either partial or mixed seizure disorders, and is also recommended in certain types of treatment refractory conditions (French et al., 2004a, 2004b). The compound also has a modest efficacy for treatment of obesity (Li et al., 2005), and is further being evaluated with some promise in certain forms of bipolar affective disorder (Suppes, 2002).

Similar to ACM, topiramate has a complex pharmacology, and ultimately the molecular mechanisms which underlie its beneficial effects are unknown (Shank et al., 2000). Among proposed effects is blockade of voltage dependent sodium channels (Zona et al., 1997), antagonism of glutamatergic transmission at kainate receptors (Gryder & Rogawski, 2003; Kaminski et al., 2004), and potentiation of GABA signaling, possibly through increased GABA availability (White et al., 1997). Anti-epileptic drugs have recently been proposed to largely fall into 2 categories, one in which GABA-potentiating effects dominate, and one in which attenuation of glutamate function is a key mechanism. When topiramate recently was evaluated with respect to this dichotomy, it was concluded on the basis of its side effect profile that it most likely falls into the GABA-ergic category. The same evaluation concluded that side effects were more common and pronounced with topiramate than with other novel anti-epileptic drugs (Roberts et al., 2005).

Based on the central role of neuroadaptations which recruit a hyperglutamatergic state in alcohol dependence (De Witte et al., 2003), beneficial effects of shifting the glutamatergic excitation–GABA-ergic inhibition balance in an inhibitory direction would not be unexpected in treating alcoholism. In fact, another prototypical anti-epileptic drug, carbamazepine, not only provides some degree of protection from alcohol withdrawal manifestations, but also may reduce relapse rates (Mayo-Smith, 1997). More specifically, it has been proposed that simultaneous potentiation of GABA function and antagonism of glutamate transmission would be beneficial in alcohol dependence by down-modulating EtOH induced dopamine release in ventral striatum (Johnson, 2004a). However, data to demonstrate this are not available. In fact, the very limited preclinical literature does not even support an efficacy of topiramate for reduction of alcohol drinking (Gabriel & Cunningham, 2005). What we are left with are 2 human reports from the same group, wherein topiramate has been shown to decrease alcohol use (Johnson et al., 2003) and to reduce negative consequences of drinking in parallel with reduction of drinking (Johnson et al., 2004). An additional secondary analysis recently published separately also indicated reduction of smoking in alcohol dependent subjects receiving topiramate (Johnson et al., 2005).

In summary, it is difficult to assess whether topiramate will provide a useful addition to the treatment toolkit in alcohol dependence, since mechanistic understanding at the preclinial level is largely lacking, as is independent confirmation of clinical efficacy, while clinical management and tolerability are more challenging with topiramate than with the currently available medications, as shown by reports of specific language impairments such as verbal fluency and word finding difficulties (Ojemann et al., 2001; Lee et al., 2003).

4. The third wave: novel treatment targets

4.1. Animal models for target discovery and validation

First and second wave pharmacological treatments for alcoholism were defined as having demonstrated efficacy in humans in some fashion. It is more challenging to identify a third wave of compounds *predicted* to be effective in humans. Many animal paradigms in current use model various characteristics of alcoholism, but we are only beginning to use them effectively to differentiate clinically effective from clinically ineffective compounds (Egli, 2005; Heilig & Egli, 2005). How, then, are we to identify compounds predicted to reduce craving, relapse and drinking in alcoholics? Many animals will drink alcohol in low to moderate amounts for its gustatory or caloric properties or for the modest positive reinforcing effects of its acute pharmacological actions. Showing that a medication reduces EtOH voluntary consumption under these conditions, however, reveals little information as to whether this medication will effectively reduce drinking, craving and relapse in alcohol dependent patients. This is because numerous medications known to be ineffective in alcohol dependent patients are capable of reducing basal alcohol drinking in animals without a history of dependence, or excessive drinking resulting from genetic selection.

Testing medication effects in paradigms which model features of addiction, such as excessive, compulsive and persistent ingestion patterns, and those which model conditions which precipitate craving and relapse are likely to be more informative. These paradigms reflect biological targets and mechanisms relevant to an alcoholism medication's therapeutic efficacy. The validity of this approach will be further supported as additional medications are tested in human alcoholics. The 4 most widely used approaches are briefly described below.

Selective breeding increases the frequency of alleles affecting alcohol preference and intake, and models genetic susceptibility to high voluntary alcohol intake, and by extension presumably also for developing alcohol abuse and alcoholism. The AA (Finland), P, HAD (US), sP (Italy), and UChB (Chile) are the most extensively studied selectively-bred alcohol-preferring rat lines. To varying degrees, these strains exhibit behavioral and physiological characteristics reported in children of alcoholics, alcohol abusers, and alcoholics, as compared with non-drinkers or light drinkers. In addition to high EtOH intake and preference, selectively bred alcohol-preferring rats display phenotypic characteristics

found in human alcoholism including altered function of serotonin and dopamine systems (Murphy et al., 2002).

Rats made tolerant, and thus physically dependent to alcohol increase their alcohol drinking during the first 12 hr following withdrawal reflecting the alleviation of acute withdrawal symptoms. Following prolonged exposure, self-administration increases for a longer time provided they are given the opportunity to self-administer EtOH 12 hr post-withdrawal (Roberts et al., 2000a). Repeated cycles of EtOH vapor exposure and withdrawal lead to a marked increase in drinking and operant self-administration which has been shown to persist months after abstinence symptoms subside (Rimondini et al., 2002). The neuroadaptively driven transition to a persistent state of high alcohol drinking emulates the clinical indications of alcoholism in that patients are most vulnerable to relapse long after acute withdrawal. Microdialysis studies reveal a progressive increase in excitatory amino acids with repeated EtOH intoxication and withdrawal episodes (Dahchour & De Witte, 2003).

When a period of alcohol access is followed by forced alcohol abstention and then access to EtOH is reintroduced, a transient period of increased drinking is observed for a day or 2. This alcohol deprivation effect (ADE) is strengthened and prolonged by repeated deprivations when used in some strains of selectively bred alcohol-preferring rats (e.g., P and HAD, but not AA). The ADE resembles in some aspects the dependence-induced drinking that occurs following cycles of EtOH vapor exposure and abstinence, but physiological dependence is not required for the ADE, and it is presently unclear whether these 2 excessive drinking phenomena involve overlapping biological substrates. The ADE has limitations in its resemblance to human alcoholism in that abstinence conditions are experimentally imposed. Nevertheless, this model may capture aspects of binge drinking following relapse. Although the neuronal circuits involved in the ADE are not well known, NMDA receptors are implicated in the expression of increased drinking under these conditions (Vengeliene et al., 2005).

Finally, it is possible to model environmental conditions that precipitate craving and relapse using the reinstatement paradigm. The reinstatement paradigm measures the ability of environmental or pharmacological stimuli to reinstate previously reinforced operant responding when alcohol is no longer available. This paradigm models the previously discussed conditions which precipitate craving and relapse such as acute alcohol priming, the presence of cues predictive of alcohol availability, and stressors. The mechanisms by which drugs prevent reinstatement of alcohol seeking have been pharmacologically dissociated from those that reduce drinking (Liu & Weiss, 2004). The receptor systems involved in these 3 types of relapse triggers (i.e., priming, cues, and stress) have also been differentiated pharmacologically. Stress-induced reinstatement appears to involve Corticotropin Releasing Factor (CRF) and 5HT circuitry originating in the median raphe nucleus (Le et al., 2000) whereas cue induced reinstatement involves the mesolimbic and prefrontal cortical DA system (Katner & Weiss, 1999). This latter observation is consistent with findings from human laboratory fMRI studies of craving (Myrick et al., 2004).

Superficially, it might be expected that more pronounced and persistent manifestations of a clinical indication such as heavy drinking or reinstatement would be more resistant to pharmacotherapy than weaker manifestations of the same indication. Using this reasoning, an effective medication would be expected to reduce light to moderate drinking by a non-dependent animal more effectively than heavier drinking by dependent or genetically predisposed animals. Emerging evidence is proving this assumption to be wrong. For example, ACM administration reduces alcohol drinking by alcohol dependent rats (Rimondini et al., 2002), prevents or blocks the ADE (Spanagel et al., 1996; Heyser et al., 2003), and reduces alcohol-seeking evoked by environmental cues predictive of alcohol availability (Bachteler et al., 2005). By contrast, ACM effects on voluntary alcohol drinking by non-dependent light-drinking rats are minimal. The third wave targets discussed below have demonstrated efficacy in behavioral models which manifest the influence of distinct genes, systems, and circuitry associated with the alcoholism phenotype.

4.2. Cannabinoid CB_1 receptor antagonism

Key components of the endocannabinoid system are at least 2 G-protein-coupled receptors, endogenous endocannabinoids, including anandamide (AEA) and 2-arachindonylglycerol (2-AG), and the endocannabinoid degrading enzyme fatty acid amide hydrolase (FAAH). The main neuronal endocannabinoid receptor subtype, the CB_1 receptor, is widely distributed in the CNS, with high density in the cortex, hippocampus, basal ganglia and cerebellum.

The role of endocannabinoids in EtOH intake was elegantly demonstrated in a study showing that high EtOH intake by C57Bl/6J mice was reduced by CB_1 receptor blockade to levels consumed by CB_1 receptor null mutant mice (Wang et al., 2003). Evidence that the endocannabinoid system might be involved in alcohol dependence appeared in a series of papers by Hungund et al. revealing that chronic EtOH vapor exposure increased brain AEA and 2-AG levels and down-regulated CB_1 receptors (Basavarajappa et al., 1998; Basavarajappa & Hungund, 1999). Whether these changes contribute to the development of alcohol tolerance is the subject of ongoing investigation.

Behavioral evidence also strongly supports a role for the CB_1 receptor in animal models of alcoholism susceptibility, dependence, and craving. CB_1 antagonist administration more effectively reduced alcohol drinking by rats with a history of EtOH dependence (Rodriguez de Fonseca et al., 1999) and by alcohol-preferring Marchigian sP rats (Cippitelli et al., 2005) compared to non-dependent Wistar rats. CB_1 antagonists have also been demonstrated to decrease the ADE (Gessa et al., 2005) and cue-induced reinstatement (Cippitelli et al., 2005) in alcohol preferring sP rats.

Elevated CB_1 receptor expression appears to contribute to phenotypes of excessive drinking. A gene screening study identified the CB_1 receptor as one of the genes whose expression is increased 3 weeks after termination of an intermittent EtOH exposure paradigm, a time period associated with a long-lasting doubling of EtOH intake (Rimondini et al.,

2002). In addition, alcohol preferring msP rats were found to have greater CB_1 receptor mRNA expression in a number of brain regions involved with reward processing and reward-associated behaviors, including the frontoparietal cortex, caudate-putamen and the CA1 and dentate gyrus areas of the hippocampus (Cippitelli et al., 2005). Consistent with the earlier alcohol vapor studies, 18 days of voluntary EtOH consumption resulted in a trend toward general CB_1 receptor down-regulation in these regions to baseline levels observed in Wistar rats. Human genetic studies support the emerging experimental hypothesis linking clinical forms of alcoholism to polymorphisms or mutations of genes encoding the CB_1 receptor (Schmidt et al., 2002) as well as to other aspects of the endocannabinoid system (Sipe et al., 2002).

Physiological evidence supports the behavioral observations implicating the CB_1 receptor in the moderate, positive-reinforcement-driven phase of alcohol drinking which occurs prior to dependence, as well as the neuroadaptively driven transition to heavy drinking after a prolonged history of alcohol abuse. CB_1 receptor knockout mice exhibit reduced voluntary alcohol drinking, compared to wildtype mice, and completely lack characteristic increases in extracellular DA in the nucleus accumbens following acute EtOH administration (Hungund et al., 2003). This finding, which should be followed up with CB_1 antagonist studies, may predict the general positive-reinforcement-dampening effects of CB_1 receptor blockade as manifested by reduced sucrose and saccharine intake, and the comparable reductions in modest EtOH intake observed in non-dependent rats (Freedland et al., 2001) CB_1 receptors also regulate glutamate release in a variety of brain structures (Schlicker & Kathmann, 2001) raising the intriguing possibility that the endocannabinoid system contributes to the hyperglutamatergic state which develops over the course of alcohol dependence (Dahchour & De Witte, 2003) and the glutamate-mediated regulation of EtOH self-administration and relapse (Backstrom et al., 2004; Spanagel et al., 2005).

The CB_1 receptor antagonist rimonabant (Acomplia®) is currently under development by the French company Sanofi-Aventis for the management of obesity (Van Gaal et al., 2005), and is currently being investigated by NIAAA researchers for its ability to reduce voluntary alcohol consumption by non-treatment seeking heavy drinkers. If it reaches the marketplace, its successful use in treating alcoholism will be facilitated by thoughtful evaluation of the clinical targets and patients subtypes most responsive to treatment. Rimonabant is reported to be well tolerated in humans; yet potential anxiety-related side effects in alcohol dependent patients remain a concern in light of the reported involvement of the CB_1 receptor in the ability to extinguish fearful memories (Marsicano et al., 2002).

4.3. Modulators of glutamatergic transmission

4.3.1. mGluR5 antagonism

Glutamatergic neurotransmission plays an important role in the pathogenesis of alcoholism (Tsai & Coyle, 1998; Herman, 2002). Cycles of chronic alcohol intoxication, withdrawal, abstinence, and relapse recruit a hyperglutamatergic state in brain regions associated with alcohol reward. Excessive or pathologically enhanced glutamate neurotransmission has been implicated in many neurological disorders, and may contribute to increased EtOH intake and vulnerability to relapse in alcoholics as suggested by the *per2* knockout study discussed earlier. Hence, diminishing the consequences of excessive glutamatergic activity may be a fruitful pharmacotherapeutic strategy for reducing alcohol abuse, craving and relapse.

Ionotropic glutamate receptors have a well established role in addiction, but have proven to be difficult targets for pharmacotherapies because of their fundamental role and ubiquitous distribution. Modulating glutamatergic transmission by targeting pre- or postsynaptic metabotropic glutamate receptors (mGluRs) may offer an attractive alternative with a better safety profile (Costantino et al., 2001). Of the several mGluR subtypes, the mGluR5 and mGlu2/3 receptors are abundant in mesocorticolimbic brain regions associated with drug reinforcement. The role of mGluR5 in drug reinforcement was first confirmed in a study showing that mGluR5 null mutant mice do not self-administer cocaine (Chiamulera et al., 2001).

Mechanistic hypotheses regarding mGluR5's potential influence on EtOH action are emerging through evidence of functional postsynaptic interactions between the mGluR5 and ionotropic NMDA receptors, whose role in EtOH's behavioral and physiological actions are well characterized (Kotecha et al., 2003). Synaptic transmission at the NMDA receptor is enhanced by simultaneous activation of mGluR5 via phosphorylation by PKC (Hermans & Challiss, 2001). This suggests that blockade of mGluR5 could reduce glutamatergic signaling through NMDA receptors and thereby alleviate glutamatergically driven behavioral characteristics of alcoholism.

mGluR5 antagonists appear to be exclusively effective in reducing excessive, but not moderate or low-level drinking. Subchronic administration of the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP) failed to reduce baseline EtOH self-administration by non-dependent Long-Evans rats, while the same dose range reduced alcohol self-administration by alcohol-preferring P rats, reduced the expression of the ADE in both Long-Evans and P rats, and reduced cue-induced reinstatement of lever pressing for EtOH (Backstrom et al., 2004; Schroeder et al., 2005). A subsequent study replicated the finding that mGluR5 blockade reduced alcohol self-administration by P rats, this time using inbred P rats and an mGluR5 antagonist, 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]-pyridine (MTEP), that has a greater selectivity for the mGlu5 receptor (Cowen et al., 2005). Additional pharmacological tools may be needed to fully characterize the role of mGluR5 receptors in mechanisms of alcohol dependence, as both MPEP and MTEP have been shown to possess effects other than those mediated through antagonism at this receptor type (Lea et al., 2005).

Potential therapeutic mechanisms for MPEP's effects in alcoholism models abound. MPEP administration reduced EtOH drinking by alcohol-preferring C57Bl/6 mice to the lower levels consumed by PKCε null mutant mice (Olive et al., 2005). The involvement of PKCε in reduced drinking was supported by observations that MPEP reduced basal levels of

PKCε phosphorylation at the C-terminal region, and that mGlu5 receptor densities in PKCε knockout mice were comparable to wildtype. MPEP also increases DA levels in the prefrontal cortex and nucleus accumbens (Homayoun et al., 2004), actions which have been shown to reduce EtOH self-administration (Hodge et al., 1996, 1997). The ADE depends on actions at the NMDA receptor (Vengeliene et al., 2005), suggesting the possibility that MPEP reduces the ADE through the functional coupling of the mGluR5 receptor to the NMDA receptor.

MPEP produces anxiolytic and antidepressant effects in rats (Pilc et al., 2002), raising an additional means by which alcohol drinking could have been decreased by MPEP administration. This possibility appears unlikely, however. MTEP reduced EtOH self-administration by alcohol preferring Fawn-Hooded rats, an animal model of comorbid depression and alcohol-seeking, at doses which failed to reduce measures of anxiety and depression (Cowen et al., 2005).

The compelling profile for mGluR5 in animal models of alcoholism is bolstered by recent observations that ACM has functional mGluR5 properties (Harris et al., 2003). This provides indirect clinical validation for mGlu5 antagonism as an effective therapeutic mechanism for alcoholism treatment. A final caveat should be noted, however. Reduced drinking by P rats following MTEP administration was associated with sedation, whereas no sedative effects were noted for MPEP, an mGlu5 antagonist with a number of "off target" actions including NMDA receptor antagonism, norepinephrine transporter inhibition, and modulation of the mGluR4 receptor. Clearly, selectivity is not automatically a blessing.

4.3.2. mGluR2/3 agonism

Group II mGluR receptor ligands offer another approach to reducing excessive glutamatergic neurotransmission and have characteristics which recommend exploring their use for treating alcohol dependence. Similar to the mGluR5 receptor, mGluR2/3 receptors are expressed preferentially in mesocorticolimbic brain regions implicated in EtOH self-administration and dependence (Schoepp, 2001). Numerous examples from neuropsychopharmacology suggest that modulation of endogenous transmission by targeting presynaptic transporters or autoreceptors may have advantages over directly targeting postsynaptic sites. mGluR2/3 receptors are located both pre- and postsynaptically, but presynaptic autoreceptor function appears to be the most germane to their potential therapeutic action. Indeed, in vivo microdialysis studies revealed that stimulation of mGluR2/3 receptors reduced extracellular glutamate levels in the nucleus accumbens, whereas receptor blockade increased extracellular glutamate (Xi et al., 2002).

Of additional potential significance to alcohol dependence, mGluR2/3 agonists have a solid anti-stress, anti-anxiety profile, the significance of which will be discussed more extensively in the next section. The selective mGlu2/3 agonist (1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) has been shown to be an effective anxiolytic agent in a battery of animal models including fear-potentiated startle, elevated plus maze, conflict drinking, stress-induced hypothermia, and a lactate-induced panic-like response (Marek, 2004). A recent study revealed that anxiolytic effects of LY354740 administration were completely absent in mGluR2 and mGluR3 null mutant mice (Linden et al., 2005), suggesting that activity at both mGluR2 and mGluR3 receptors is required of the compound's anxiolytic effects.

The possible value of mGluR2/3 agonists in the treatment of drug craving was supported by a study showing that the mGlu2/3 agonist selectively blocked cue-induced cocaine reinstatement (Baptista et al., 2004). Recent publications reported the predictable observation that an mGlu2/3 *antagonist* had no effect on EtOH self-administration by P rats and C57 mice (Schroeder et al., 2005; Hodge et al., 2006). More recently, however, the mGluR2/3 agonist LY404039 was reported to reduce expression of the ADE and EtOH craving in P rats at doses which did not affect basal EtOH self-administration (McKinzie et al., 2005).

LY354740 has already demonstrated clinical efficacy for generalized anxiety disorder in a multi-center study supported by Eli Lilly and Company (Marek, 2004). As mentioned above, co-morbidity between alcohol dependence and anxiety disorders is extensive. Futhermore, currently available anxiety treatments, such as benzodiazepines, are not attractive for use in alcohol dependent subjects beyond acute abstinence because of their abuse liability. mGluR2/3 agonists may therefore become valuable for clinical management of alcoholism independently of their ability to affect drinking. In addition, theoretical considerations outlined here suggest the possibility that this class of drugs may also be beneficial for the core symptoms of alcoholism. A potential concern may be related to recent reports of impaired cognitive function resulting from mGluR2/3 agonism in animals (Higgins et al., 2004), but human experience so far does not support this concern. The development of mGluR2/3 agonists for anxiety disorders by major pharmaceutical companies will markedly facilitate their evaluation and development for other indications, such as alcohol dependence. Further testing of mGlu2/3 agonists in animal models of alcoholism, and early Phase II studies in an appropriate sample of alcohol dependent patients would be highly valuable.

4.4. Stress-related neuropeptides

4.4.1. Corticotropin-releasing factor

Efforts to understand the neurobiological and motivational underpinnings of alcohol abuse and addiction have emphasized the positive reinforcement and pleasurable hedonic brain circuitry activated by EtOH's pharmacological actions. Although these systems are clearly important in the early stages of alcohol dependence, patients are more likely to seek treatment in later stages of dependence, impelling an examination of targets operative after alcohol abuse patterns have been well engrained. As discussed previously, anxiety-like negative affect and mood disturbance is a hallmark of alcoholism, whether it is present as a dispositional comorbidity, emerges as an acquired symptom of chronic alcohol abuse, or is elicited by acute or chronic external stressors. As discussed in the previous section, the capability to reduce anxiety through pharmacotherapy is a desirable treatment objective, especially by targeting those

substrates which also contribute to excessive drinking and craving in dependent patients.

CRF systems mediate a broad range of stress and anxiety responses which are reversed by CRF1 antagonist administration (Britton et al., 1986). Acute EtOH withdrawal produces anxiety-like responses which are correlated with increased CRF levels in the CeA (Merlo Pich et al., 1995) and in the bed nucleus of the stria terminalis (Olive et al., 2002) and which are reversed by non-selective CRF antagonist administration (Baldwin et al., 1991). These findings provide a solid preclinical foundation for the prediction that CRF antagonist treatments might be useful for alleviating withdrawal-induced anxiety, and relapse driven by acute withdrawal symptoms.

Most relapse occurs months after cessation of acute withdrawal symptoms, however. A crucial issue is, therefore, whether there is reason to believe that CRF antagonism treatment might also be beneficial for long-term relapse prevention. Although less direct than the evidence for blockade of withdrawal-induced drinking, several observations indicate that this might indeed be the case. Many neuroadaptive responses to chronic EtOH intoxication and withdrawal persist after acute withdrawal symptoms have subsided and are associated with anxiety and other negative affect, a phenomenon called protracted abstinence. CRF's involvement in distinct acute and protracted abstinence phases was illustrated in a study showing markedly reduced CRF levels in the amygdala during the first day after EtOH withdrawal which then progressively increased to levels which were nearly double that of non-dependent rats when measured 6 weeks post-withdrawal (Zorrilla et al., 2001). EtOH drinking increases during both post-withdrawal time periods; however, 2 distinct processes involving CRF may be at work, one reflecting acute withdrawal effects and the other a delayed and more persistent process.

Subsequently, it was shown that a history of dependence renders animals more sensitive to anxiolytic-like effects of D-Phe-CRF. Stress-induced anxiety responses were diminished by D-Phe-CRF administration in rats with a history of ethanol dependence, but no effect was seen in a less anxious control group which had not been previously exposed to EtOH (Valdez et al., 2003). Consistent with these findings, the non-selective CRF antagonist D-Phe-CRF reduced elevated EtOH self-administration during protracted abstinence to levels below that of control rats (Valdez et al., 2002). The relationship between CRF-antagonist reduction of EtOH drinking and concurrent anxiolytic action may be complex, however. The CRF1 receptor antagonist antalarmin reduced anxiety and ongoing EtOH drinking by fawn-hooded rats; however, diazepam also reduced anxiety to a comparable degree, yet failed to reduce established EtOH drinking (Lodge & Lawrence, 2003).

Stress exposure during abstinence increases alcohol craving and susceptibility to relapse after treatment completion, suggesting that attenuating stress-related alcohol craving through pharmacological interventions could be a relevant target in the development of new treatments for alcohol dependence (Breese et al., 2005). CRF antagonists have been shown to selectively attenuate stress-induced, but not cue-induced craving in reinstatement studies of rats with a history of alcohol dependence (Liu & Weiss, 2002). Stress-induced reinstatement of alcohol-seeking is mediated by CRF through extrahypothalamic substrates (Le et al., 2000), specifically through 5HT cell bodies in the median-raphe-nucleus (MRN). The possible involvement of MRN projections to the central nucleus of the amygdala (CeA) was supported by showing that intra-MRN infusions of D-Phe-CRF blocked footshock-induced increases in c-fos mRNA in the CeA (Funk et al., 2003).

Although prolonged alcohol abuse engenders anxiety and negative affect which is believed to drive further alcohol abuse, dispositional anxiety may also contribute to alcohol abuse and dependence. Animal models of genetic susceptibility to alcohol abuse suggest a role for CRF in anxiety-based vulnerability to drink alcohol, but available evidence does not support a simplistic "more CRF equals more anxiety and more alcohol preference" model. Thus, alcohol-preferring P rats have significantly *lower* brain CRF concentrations relative to alcohol non-preferring NP rats (Ehlers et al., 1992). Reduced CRF expression in the central nucleus of the amygdala (CeA) correlated with higher anxiety in P rats relative to NP rats (Hwang et al., 2004). In contrast, alcohol-preferring sP rats have elevated dialysate CRF levels in the CeA and heightened anxiety compared to sNP rats (Richter et al., 2000).

Preliminary data suggest that the CRF antagonist antalarmin reduces EtOH drinking by P rats (Richard Bell and Lucinda Carr, unpublished observations) and by msP rats (Roberto Ciccocioppo and Markus Heilig, unpublished observations). Genetic manipulations in mice also support the involvement of CRF in a dispositional alcohol drinking phenotype. CRF null-mutant mice drink twice as much EtOH as their wildtype counterparts (Olive et al., 2003) whereas CRF overexpressing mice show reduced EtOH drinking and preference (Palmer et al., 2004). Although this might seem contrary to expectation, deletion and overexpression of CRF in these studies were constitutive, with the usual possibility of activating compensatory mechanisms. Loss of function in the CRF1 gene was associated with upregulation of the NMDA NR2B subunit and a delayed and persistent enhancement of EtOH drinking following repeated stress exposure suggesting a genetic vulnerability factor which is mediated by environmental conditions (Sillaber et al., 2002).

Although the emerging picture is by no means simple, the foregoing evidence recommends CRF receptors as key targets for developing pharmacological treatment for alcohol dependence. Until recently, efforts have mainly focused on the CRH1 receptor. The ongoing characterization of the role of urocortin, an endogenous ligand for the CRF2 receptor, in EtOH drinking suggest that the CRH2 subtype may also offer a potential target (Ryabinin et al., 2002). Treating alcohol-dependent rats with urocortin III (a CRF2 agonist) reduced anxiety and EtOH self-administration in the early stages of withdrawal (Valdez et al., 2004).

An obvious potential limitation to successful targeting of the CRH system is the concern that sustained pharmacotherapy with CRF1 and CRF2 agents might have undesirable hormonal and affective side effects. For instance, mutant mice lacking

CRF1 receptors, CRF2 receptors, or both, have impaired stress responses and abnormal anxiety-like behaviors (Smith et al., 1998; Bale et al., 2000, 2002). In their review of therapeutic potential of CRF1 antagonists for anxiety disorders, Zorrilla and Koob (2004) concluded that Phase I and Phase II trials with CRF1 compounds have not yielded evidence of HPA-axis insufficiency, other endocrine disturbance, or significant adverse events. Nevertheless, as clinically promising CRF1 antagonists become available for testing in alcohol dependent patients, it will be important to monitor anxiety and hormonal responses over the course of treatment.

4.4.2. Neuropeptide Y

Neuropeptide Y (NPY) is widely distributed in the CNS, is concentrated in limbic and cortical areas, and is involved in a variety of biological functions. It was initially identified as having orexogenic effects through action in the hypothalamus (Stanley & Leibowitz, 1985) and subsequently found to have various anxiolytic effects through distinct actions in the CeA (Heilig et al., 1993). This suggested 2 avenues by which NPY could influence EtOH drinking. As discussed previously, EtOH drinking can be viewed as an appetitive phenotype, as well as a stress and anxiety driven phenotype depending on patient subtype and stage of EtOH dependence. Initial evidence strongly pointed to NPY's involvement in stress and anxiety mediated EtOH drinking in that a clear inverse relationship between NPY expression and EtOH drinking was shown in NPY knockout and transgenic mouse studies (Thiele et al., 1998). This inverse relationship is widely supported, although NPY administration has the ability to increase moderate EtOH drinking, possibly for caloric content, through its hypothalamic actions (Kelley et al., 2001).

Genetic analysis in P and NP rats revealed a quantitative trait locus in a chromosomal region which includes the NPY gene (Bice et al., 1998; Carr et al., 1998). Subsequent studies revealed that P and HAD rats (Ehlers et al., 1998; Hwang et al., 1999; Suzuki et al., 2004), and EtOH-preferring C57Bl/6J inbred mice (Hayes et al., 2005) have lower NPY expression in the CeA relative to non-preferring strains. NPY Y2 receptor expression in the medial amygdala of EtOH-preferring AA rats was reduced relative to ANA and Wistar rats, whereas EtOH non-preferring ANA rats deviate from both the AA and genetically heterogenous Wistar rats in having higher NPY expression (Caberlotto et al., 2001). In humans, an NPY gene polymorphism encoding a Leucine to Proline substitution at position 7 of the NPY signal peptide was associated with alcohol dependence in European American and Finnish alcoholics, although the nature of this association remains ambiguous (Kauhanen et al., 2000; Ilveskoski et al., 2001; Lappalainen et al., 2002). A recent haplotype-based analysis of 5 NPY polymorphisms for association with alcoholism diagnosis, or more narrowly defined phenotypes in a Swedish population revealed a protective effect of a haplotype present in about 5% of the population (Mottagui-Tabar et al., 2005). This protective effect was further strengthened when restricted to late-onset alcoholics, characterized by anxious personality traits. The protective haplotype is likely a gain of function variant, making these findings consistent with the animal literature and suggesting that NPY-based pharmacotherapy may be particularly useful in a subpopulation of susceptible patients. Consistent with this hypothesis, NPY administration markedly reduces enhanced EtOH drinking in P and HAD rats (Badia-Elder et al., 2001, 2003). With few exceptions, however, NPY administration fails to change moderate EtOH consumption by Wistar rats (Slawecki et al., 2000; Caberlotto et al., 2001; Katner et al., 2002a, 2002b). Recent studies suggest that sensitized brain NPY systems are associated with the ADE in P rats. A single NPY injection administered prior to reintroducing EtOH after 2 weeks markedly reduced EtOH drinking for 3 days (Gilpin et al., 2003). NPY-stimulated feeding was found to be greater following an EtOH deprivation period relative to that of a non-deprived control group (Gilpin et al., 2005).

Central NPY expression is recruited in an adaptive, opposing-process stress response, mimicked by the pharmacological actions of NPY. NPY and CRF systems may interact to influence EtOH dependence through their neuroanatomical association in the CeA which contribute to opposing actions on a variety of anxiety and stress dimensions (Sajdyk et al., 2004). Recent findings are consistent with earlier evidence that NPY may act as a functional CRF antagonist (Ehlers et al., 1997). NPY administration greatly reduced EtOH drinking by rats with a history of dependence and completely reversed suppression of EtOH intake produced by CRF administration regardless of the rat's dependence history (Thorsell et al., 2005). This observation raises the hypothesis that NPY action reduces dependence-induced drinking by reducing anxiety resulting from increased amygdalar CRF levels reported during protracted EtOH abstinence, in addition to normalizing dysregulated NPY systems associated with vulnerability and dependence.

At least 4 G-protein coupled receptors for NPY have been identified, and 3 of these, Y1, Y2, and Y5, have been shown to influence EtOH ingestion (Schroeder et al., 2003a,b; Thiele et al., 2002, 2004). Antisense inhibition of the Y1 receptor expression blocks the anxiolytic effects of NPY in the amygdala recommending this receptor as a target for reducing relief-seeking driven alcohol drinking (Heilig & Widerlöv, 1995). The Y2 receptor functions as a presynaptic autoreceptor and presumably blocks NPY signaling via the Y1 and other post-synaptic receptors, supporting the use of Y2 antagonist administration to reduce dependence-induced drinking. The Y2 antagonist BIIE0246 selectively reduced operant EtOH self-administration by non-dependent Wistar rats, but BIIE0246 was far more potent in rats with a history of dependence induced by long-term intermittent exposure to EtOH vapor (Thorsell et al., 2002; Rimondini et al., 2005).

In a heuristically rich hypothesis proposed by Valdez and Koob (2004), NPY levels rise and opposing CRF levels fall following EtOH ingestion, and return to baseline levels soon thereafter. As dependence progresses, however, neither system is capable of returning to baseline, resulting in elevated CRF and diminished NPY outside of the homeostatic range. This long-term allostasis is hypothesized to lead to behavioral pathologies associated with continued alcohol drinking and relapse, with CRF contributing to a persistent negative affect,

and NPY providing the relief-motivated basis for drinking. By implication, an effective pharmacotherapy would be predicted to restore these mutually opposing systems to homeostatic levels.

Despite the strong empirical and theoretical justification for targeting NPY receptors in the development of pharmacotherapy for alcoholism, these efforts are hampered by the dearth of non-peptide ligands with suitable properties. Many of the emerging investigational NPY drugs are being developed to treat obesity, and, as implied the foregoing discussion, these agents block NPY action, whereas reducing EtOH drinking, craving, and dependence related anxiety, may require enhanced functioning of NPY in the amygdala. The development of NPY-based medications for alcohol dependence would be greatly advanced by giving these targets higher priority in ongoing molecular synthesis and small molecule screening efforts. Among such efforts, development of Y2 antagonists may be the strategy with the highest chances of success.

4.4.3. Nociceptin

The nociceptin/orphanin FQ (N/OFQ) peptide is the endogenous ligand for the NOP receptor. It is structurally similar to the opioid peptide dynorphin, but does not bind to μ-, δ-, or κ-opioid receptors, neither do opioid peptides bind to the NOP receptor. Nevertheless, N/OFQ has a number of anti-opioid actions including the ability to block the analgesic effects of selective μ-, δ-, or κ-opioid agonists (Mogil et al., 1996), to attenuate the development of tolerance to morphine analgesia (Lutfy et al., 2001), and to antagonize morphine's motivational effects (Murphy et al., 1999). NOP receptors are located in brain areas associated with motivation and addiction (e.g., amygdala, mPFC, VTA, lateral hypothalamus, BNST, nucleus accumbens). In addition, N/OFQ decreases dopamine transmission in the nucleus accumbens by inhibiting dopamine neuronal activity in the VTA (Murphy & Maidment, 1999), an action predicted to block the positive reinforcing effects of drugs. These characteristics prompted researchers at the University of Camerino, Italy to investigate whether N/OFQ could reduce alcohol drinking and craving in animal models.

As is the case with other third wave compounds, a positive signal for possible therapeutic efficacy was enhanced when N/OFQ was examined in models of excessive, rather than low-level or moderate drinking. Specifically, N/OFQ reduced EtOH drinking by genetically selected msP rats, but had no effect on EtOH drinking by Wistar rats (Ciccocioppo et al., 2004b; Fedeli et al., 2004). Furthermore, N/OFQ blocked the ability of an olfactory cue to reinstate extinguished alcohol-seeking by msP rats (Ciccocioppo et al., 2004b). Another research team found that N/OFQ surpassed naloxone in its ability to block the acquisition and expression of EtOH conditioned place preferences in mice, an alternative measure of EtOH reward (Kuzmin et al., 2003).

The foregoing profile might suggest that targeting the NOP receptor would merely offer an interesting alternative to the μ-opioid receptor for producing a NTX-like therapy for alcoholism, although the outcome might be predicted to be somewhat superior. Additional characteristics of N/OFQ suggest additional advantages over opiate antagonist treatment, however. N/OFQ appears to also play an important role in the regulation of stress responses (Devine et al., 2001) and exerts anxiolytic and anti-stress actions over the dose range which reduces EtOH drinking (Jenck et al., 1997). Specifically, in addition to acting as a functional opioid antagonist, N/OFQ appears to act as a functional CRF antagonist, blocking CRF's anorectic effects through action in the BNST (Ciccocioppo et al., 2004a), suggesting that N/OFQ might also effectively alleviate stress related alcohol craving. This was confirmed in a study showing that N/OFQ prevented foot-shock-induced reinstatement of alcohol-seeking, but did not affect cocaine-seeking behavior (Martin-Fardon et al., 2000). Whether N/OFQ reduces the "relief-seeking" driven elevation in drinking during protracted abstinence through its functional CRH-antagonist actions remains the subject of ongoing investigation.

Although relapse-inducing stimuli can be differentiated experimentally, abstinent alcohol dependent subjects most likely encounter environments in which diverse constellations of relapse triggers are present. The impact of this environmental complexity on craving and medication efficacy was demonstrated in a study by Liu and Weiss. Footshock stress and alcohol-predictive cues presented together interacted to increase the likelihood and intensity of alcohol-seeking lever pressing relative their effects when presented alone (Liu & Weiss, 2002). Under these conditions, neither CRF-antagonist nor opioid-antagonist administration was sufficient to completely eliminate alcohol-seeking. Rather, it was necessary to co-administer the CRF antagonist and opioid antagonist to completely abolish reinstatement of alcohol seeking. These findings suggested the diminished efficacy of medications having highly specific opioid or CRF actions in the presence of the heterogeneous relapse-inducing environmental conditions more typical of a patient's environment. Because of its combined functional opiate and CRF antagonism, N/OFQ is predicted to have superior efficacy to NTX or CRF1 antagonists under these conditions. This prediction remains to be experimentally tested. In addition, while blocking the emotional effects of CRF, N/

Table 2
Outcomes of testing third wave target compounds in animal models of alcoholism

	CB1	mGluR5	mGluR2/3 [a]	CRF	NPY	N/ORQ
EtOH Preferring (baseline drinking)	yes	yes	no	yes	yes	yes
Dependence Induced Drinking	yes	N/A	N/A	yes	yes	N/A
Alcohol Deprivation Effect	yes	yes	yes	N/A	yes	N/A
Reinstatement	yes	yes	yes	yes	N/A	yes
Clinical Testing (other disorders)	yes	yes	yes	yes	yes [b]	yes [c]

Yes = data in this model are consistent with predicted clinical efficacy; No = no effect reported; N/A = tests in this model not available in the literature.

[a] Preliminary findings. mGluR2/3 drugs have not been tested extensively in alcoholism models.

[b] NPY *antagonists* have been tested for obesity.

[c] N/ORQ agonists and analogues have been administered peripherally to treat pain.

OFQ does not appear to interfere with HPA-axis response to stress (Devine et al., 2001). Antagonism of CRF and opioid receptors, on the other hand, has actions which may impair desirable beneficial responses to stressors.

Studies on the N/OFQ-NOP system and alcohol action have been performed via central administration of the N/OFQ peptide. A number of non-peptide agonists for the NOP receptor have been synthesized (Rover et al., 2000). The foregoing evidence highly recommends that orally effective NOP agonists be identified and tested in animal models of alcoholism, and developed for subsequent human testing.

5. Conclusion

Lessons learned from each wave of compounds will facilitate the development of additional medications. To be successfully marketed and widely prescribed in appropriate patients, first wave compounds will need to overcome multiple barriers such as lack of patient awareness and misperceptions concerning efficacy and side effects. Once these obstacles are overcome, it will be easier to navigate these potential barriers more efficiently as second wave target compounds become available. In addition, first wave compounds will not be effective in all patients. Practices will emerge which facilitate the rapid and efficient identification of treatment efficacy and responsive patient profiles, possible through the discovery of biomarkers and through pharmacogenomic approaches. These practices will promote more efficient testing and, it is hoped, wider use of second wave compounds which, in turn, will engender a more positive opinion of their therapeutic value.

Second wave compounds comprise a broader range of therapeutic targets. Ongoing testing of these medications in patients will potentially reveal additional therapeutic mechanisms of action for treating alcohol dependence, and identify new patient subtypes. These compounds will also be invaluable to validating preclinical testing approaches leading to the discovery of additional third wave compounds. Of the second wave compounds reviewed above, only baclofen has received extensive testing in animal models of alcoholism. Testing these compounds in animal models would provide the opportunity to compare preclinical and clinical responses in order to identify signals in preclinical evaluations which predict clinical efficacy.

The animal laboratory models reviewed above are beginning to yield pharmacological profiles, summarized in Table 2 to the extent available today, can facilitate the rapid conversion of third wave targets to second wave compounds. Compounds for many of the third wave targets are currently being tested in humans for conditions other than alcoholism, and the data presented here provide compelling justification for testing them in alcohol dependent patients.

In conclusion, based on the information reviewed here, we predict that the coming decade holds considerable promise to see a series of novel pharmacodynamic principles be added to the toolkit available for treatment of alcohol dependence. This development has the potential of reshaping the perception of alcoholism among patients, health care professionals and policy makers alike, something which is long overdue, and critical to improving clinical care to the extent that the science allows. If, but only if, the novel treatments are broadly implemented and supported, it will become feasible to markedly improve clinical outcomes in alcoholism.

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